

# The relation of body size to plasma levels of estrogens and androgens in premenopausal women (Maryland, United States)

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We analyzed data from a cross-sectional study of 107 premenopausal women to evaluate the relations of height, weight, and body mass index (BMI) with plasma hormone levels. Participants were 20- to 40-year old women residing in Maryland (United States), whose reported menstrual cycle lengths were not more than 35 days and whose measured weights for height were 85 to 130 percent of 'desirable' based on 1983 Metropolitan Life Insurance tables. Fasting blood specimens were collected on each of days 5-7, 12-15, and 21-23 of every participant's menstrual cycle and pooled to create follicular, midcycle, and luteal phase samples, respectively, for analysis. Adjusted for age, taller women had significantly higher follicular-phase plasma-estradiol levels (percent difference/cm = 1.5, 95 percent confidence interval [CI] = 0.3-2.7, and heavier women had significantly lower plasma sex-hormone binding globulin (SHBG) levels averaged across the menstrual cycle phases (percent difference/kg = -1.2; CI = -1.9--0.6). Body weight within the range studied, however, was not related significantly to the concentration of SHBG-bound estradiol during any phase of the menstrual cycle. The results of this cross-sectional study suggest a possible mechanism by which height may influence breast cancer risk. *Cancer Causes and Control* 1995, 6, 3-8.

**Key words:** Androgens, estrogens, height, weight, United States.

## Introduction

The relation of anthropometric measurements to breast cancer risk has been investigated extensively. Height is associated positively with risk in many<sup>1-8</sup> but not all<sup>9-11</sup> studies. Body weight also is reported to exhibit a direct<sup>4,7,10-16</sup> or null<sup>3,6,8,9</sup> relation to breast cancer risk in postmenopausal women. In premenopausal women,

an inverse association between body weight and breast cancer is reported by many investigators.<sup>5,6,8,9,12,14,16,17</sup> Hormones, particularly the estrogens, are believed to play a key role in the etiology of breast cancer,<sup>18</sup> and body size could modify breast cancer risk through endocrine effects. We, therefore, used data from a

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cross-sectional study of premenopausal women to evaluate the relations of height, weight, and body mass index (BMI) (weight/height<sup>2</sup>) to plasma estrogens and androgens.

## Materials and methods

Participants for the cross-sectional study were recruited by posters and newspaper advertisements from communities around Beltsville, Maryland (United States) during 1988-90. Only premenopausal women aged 20 to 40 years whose weights for height were 85 to 130 percent of 'desirable' based on 1983 Metropolitan Life Insurance tables<sup>19</sup> were eligible. To participate, women had to meet the following additional criteria: (i) usual menstrual cycle length of not more than 35 days; (ii) not pregnant or lactating during the past 12 months and not taking oral contraceptives during the past six months; (iii) no history of cancer, diseases of the reproductive or endocrine system, chronic liver or gastrointestinal disease, hypertension, diabetes, nephrolithiasis, gout, or hyperlipidemia; (iv) not taking any medications other than an occasional analgesic; (v) not following a vegetarian diet; (vi) not participating routinely in strenuous physical activities; and (vii) not smoking. Because the study's primary objective was to evaluate the association of alcohol ingestion with plasma hormones, women with a wide range of drinking patterns were recruited.

All data and blood specimens were collected during a single menstrual cycle. Heights and weights of all women were measured. Blood was collected in the morning after an overnight fast. Equal volumes of plasma from days 5-7, 12-15, and 21-23 of the menstrual cycle were pooled to create, respectively, follicular, midcycle, and luteal phase specimens. All plasma specimens were stored at -70°C until hormone analyses were performed. Estrone, estradiol, and androstenedione in plasma were measured by radioimmunoassay (RIA) following solvent extraction and celite chromatography.<sup>20</sup> Estrone sulfate also was measured by RIA after solvolysis, extraction of hydrolyzed estrone, and celite chromatography.<sup>20</sup>

Dehydroepiandrosterone (DHEAS) and progesterone were measured by RIA kits (ICN-Biomedical, Costa Mesa, CA, USA) and sex-hormone binding globulin (SHBG) was measured by an immunoradiometric assay kit (Farnos Group Ltd., Oulunsalo, Finland). Percent unbound and albumin-bound estradiol were measured using centrifugal ultrafiltration,<sup>21</sup> and SHBG-bound estradiol was calculated. Coefficients of variation for replicate quality-control samples averaged: 9.5 percent for estrone; 11.1 percent for estradiol; 4.6 percent for estrone sulfate; 16.7 percent for androstenedione; 10.8 percent for DHEAS; 9.4 percent for progesterone; 10.6 percent for SHBG; and 10.6 percent for percent unbound and 8.6 percent for percent albumin-bound estradiol.

We used linear regression to evaluate the relations of height, weight, and BMI to plasma hormone levels.<sup>22</sup> All plasma-hormone concentrations were converted to the log<sub>10</sub> scale to improve normality of the distribution before analysis. All models were adjusted for age and hormone analysis batch by including age in years as a continuous variable and batch as a set of categorical (dummy) variables. We analyzed relations of plasma hormones to height, weight, and BMI, separately, as continuous variables and after categorizing measurements into quartiles. Categorization did not reveal any significant nonlinear associations and, therefore, only results of analyses of continuous variables are presented. Interactions of anthropometric variables with age were tested by including cross-product terms in models. All analyses were performed using SAS Statistical Software.<sup>23</sup>

## Results

A total of 107 women with a mean (standard deviation) age of 29.6 (±5.1) years participated in the cross-sectional study. Their heights ranged from 149.5 to 181.6 cm with a mean of 165.4 (±6.6) cm. Weights, which by design were 85 to 130 percent of 'desirable,' ranged from 40.1 to 101.7 kg with a mean of 63.6 (±11.4) kg. The restriction on weight for height also limited the range of BMIs which varied from 16.2 to 37.1 kg/m<sup>2</sup> with a mean of 23.3 (±4.1) kg/m<sup>2</sup>.

**Table 1.** Geometric means and 95% confidence intervals (CI) for plasma estrogen levels by menstrual cycle phase (MD, USA)

| Plasma estrogen levels   | Follicular |             | Midcycle |             | Luteal |             |
|--------------------------|------------|-------------|----------|-------------|--------|-------------|
|                          | Mean       | (CI)        | Mean     | (CI)        | Mean   | (CI)        |
| Estradiol (pmol/L)       | 141        | (57-346)    | 256      | (92-712)    | 254    | (93-693)    |
| Estrone (pmol/L)         | 210        | (95-465)    | 324      | (143-732)   | 314    | (135-730)   |
| Estrone sulfate (pmol/L) | 1,364      | (517-3,597) | 2,449    | (752-7,976) | 2,240  | (707-7,097) |

**Table 2.** Percent difference (95% confidence interval [CI]) in plasma estrogen levels by menstrual cycle phase related to increasing height, weight, and BMI by one unit (MD, USA)<sup>a</sup>

|                          | Estradiol (pmol/L) |            | Estrone (pmol/L) |            | Estrone sulfate (pmol/L) |            |
|--------------------------|--------------------|------------|------------------|------------|--------------------------|------------|
|                          | % Diff.            | (CI)       | % Diff.          | (CI)       | % Diff.                  | (CI)       |
| <b>Follicular</b>        |                    |            |                  |            |                          |            |
| Height (cm)              | 1.5 <sup>b</sup>   | (0.3-2.7)  | 0.7              | (-0.3-1.7) | 1.1                      | (-0.4-2.6) |
| Weight (kg)              | 0.1                | (-0.6-0.9) | 0.4              | (-0.2-1.0) | 0.3                      | (-0.6-1.2) |
| BMI (kg/m <sup>2</sup> ) | -0.8               | (-2.8-1.3) | 0.5              | (-1.1-2.2) | -0.1                     | (-2.5-2.4) |
| <b>Midcycle</b>          |                    |            |                  |            |                          |            |
| Height (cm)              | 0.6                | (-0.9-2.0) | -0.1             | (-1.2-1.0) | -0.4                     | (-2.3-1.5) |
| Weight (kg)              | 0.1                | (-0.8-1.0) | 0.3              | (-0.3-1.0) | -0.1                     | (-1.2-1.1) |
| BMI (kg/m <sup>2</sup> ) | -0.2               | (-2.5-2.2) | 1.0              | (-0.8-2.9) | 0.1                      | (-3.0-3.4) |
| <b>Luteal</b>            |                    |            |                  |            |                          |            |
| Height (cm)              | 0.7                | (-0.5-2.0) | 0.6              | (-0.5-1.7) | 0.4                      | (-1.4-2.2) |
| Weight (kg)              | 0.2                | (-0.6-1.0) | 0.3              | (-0.3-1.0) | 0.9                      | (-0.2-2.0) |
| BMI (kg/m <sup>2</sup> ) | 0.0                | (-2.0-2.1) | 0.5              | (-1.3-2.3) | 2.0                      | (-1.0-5.1) |

<sup>a</sup>Estimates from linear regression models including age and hormone analysis batch.<sup>b</sup> $P \leq 0.05$ .

Geometric-mean plasma-estrogen levels in the follicular, midcycle, and luteal phases of the menstrual cycle are shown in Table 1. In an earlier analysis of these hormone data,<sup>24</sup> we found high correlations across menstrual cycle phases for plasma androstenedione, DHEAS, and SHBG; Pearson correlations ranged from 0.72 to 0.94. We, therefore, used mean concentrations of androstenedione, DHEAS, and SHBG for the combined follicular, midcycle, and luteal phases in the current analysis. Geometric means for androstenedione, DHEAS, and SHBG, respectively, were 9 nmol/L (95 percent confidence interval [CI] = 5-17 nmol/L), 8  $\mu$ mol/L (CI = 3-18  $\mu$ mol/L), and 39 nmol/L (CI = 18-84 nmol/L).

Associations of anthropometric variables with plasma estrogen levels are presented by menstrual cycle phase in Table 2, while Table 3 shows the associations with plasma androgen levels and SHBG

averaged across the menstrual cycle. Body weight and BMI were not associated with plasma estrogens during any phase of the menstrual cycle nor with plasma androgens averaged across the cycle. SHBG levels decreased significantly ( $P < 0.001$ ) with increasing weight and BMI. However, the amount of estradiol that was SHBG-bound was not related significantly to body weight or BMI. Percent differences in SHBG-bound estradiol (pmol/L) per kg of body weight during the follicular, midcycle, and luteal phases of the menstrual cycle, respectively, were 0.01, 0.03, and 0.13.

Height was associated significantly ( $P = 0.02$ ) positively with plasma estradiol during the follicular phase of the menstrual cycle. Residuals from the regression of age and hormone analysis batch on follicular-phase estradiol are plotted against height in Figure 1 to show the relation of estradiol to height after removing age and batch effects. For each additional cm in height, there

**Table 3.** Percent difference (95% confidence interval [CI]) in plasma androstenedione, DHEAS,<sup>a</sup> and SHBG<sup>b</sup> levels averaged across the menstrual cycle related to increasing height, weight, and BMI by one unit (MD, USA)<sup>c</sup>

|                          | Androstenedione (nmol/L) |            | DHEAS ( $\mu$ mol/L) |            | SHBG (nmol/L)     |            |
|--------------------------|--------------------------|------------|----------------------|------------|-------------------|------------|
|                          | % Diff.                  | (CI)       | % Diff.              | (CI)       | % Diff.           | (CI)       |
| Height (cm)              | 0.0                      | (-0.7-0.8) | -0.7                 | (-1.9-0.5) | 0.1               | (-1.1-1.2) |
| Weight (kg)              | -0.2                     | (-0.6-0.3) | 0.0                  | (-0.7-0.8) | -1.2 <sup>c</sup> | (-1.9-0.6) |
| BMI (kg/m <sup>2</sup> ) | -0.5                     | (-1.7-0.8) | 0.6                  | (-1.4-2.6) | -3.4 <sup>d</sup> | (-5.1-1.7) |

<sup>a</sup>DHEAS = dehydroepiandrosterone.<sup>b</sup>SHBG = sex-hormone binding globulin.<sup>c</sup>Estimates from linear regression models including age and hormone analysis batch.<sup>d</sup> $P \leq 0.001$ .

was a 1.5 (CI = 0.3-2.7) percent increase in estradiol. The association of height with total estradiol did not differ by estradiol fraction; percent differences during the follicular phase for each additional cm for free, albumin-bound, and SHBG-bound estradiol were 1.5, 1.3, and 1.6, respectively. Plasma estradiol levels at midcycle and during the luteal phase also increased directly with height, but in neither of these menstrual cycle phases was the association significant.

In a previous analysis of these data,<sup>24</sup> we found a significant ( $P = 0.001$ ) positive association between alcohol and ingestion and plasma androstenedione levels. Adjustment for alcohol ingestion did not modify results reported for androstenedione in Table 3.

Ninety-nine women (93 percent) reported regular menstrual cycles during the past year and their mean usual cycle-length was 28.5 ( $\pm 2.3$ ) days. During the month on the study, 17 women (16 percent) did not have a progesterone rise of at least 3 ng/ml during the luteal phase, indicating that the cycle was anovulatory or that days 21 through 23 were not truly mid-luteal. As shown in Table 4, height and weight were not associated with the probability of a progesterone rise.

The association of height with follicular-phase plasma-estradiol was not changed when we restricted analysis to women with a progesterone rise during the luteal phase (percent difference/cm = 1.4; CI = 0.3-2.6). Additionally, mean SHBG remained significantly ( $P < 0.0001$ ) inversely related to weight (percent difference/kg = -1.5; CI = -2.1--0.8) and BMI (percent difference/kg/m<sup>2</sup> = -3.9; CI = -5.6--2.1).

As part of this study, data also were collected on usual physical activity patterns. Women who routinely

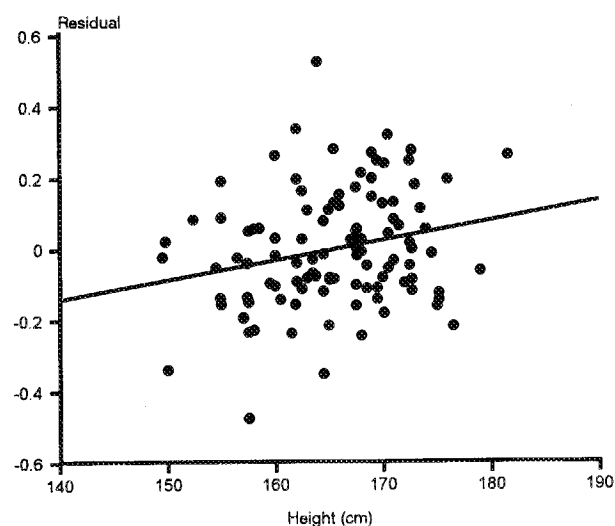


Figure 1. Relation of follicular-phase plasma-estradiol to height. Residuals from regression of follicular-phase plasma-estradiol on age and hormone analysis batch.

Table 4. Odds ratio (OR) and 95% confidence interval (CI) for a luteal-phase progesterone rise related to increasing height, weight, and BMI by one unit<sup>a</sup>

|                          | OR  | (CI)      |
|--------------------------|-----|-----------|
| Height (cm)              | 1.0 | (0.9-1.1) |
| Weight (kg)              | 1.0 | (0.9-1.1) |
| BMI (kg/m <sup>2</sup> ) | 1.0 | (0.8-1.2) |

<sup>a</sup>Estimates from logistic regression models including age and hormone analysis batch.

participated in vigorous activities were not eligible for the study, and among our fairly sedentary participants, physical activity was not associated with plasma levels of any hormones measured.

## Discussion

After menopause, heavier women have higher estrogen levels as a result of their greater adiposity and consequent increased aromatization of androgens to estrogens.<sup>25,26</sup> In premenopausal women, the ovaries, rather than adipose tissue, are the major source of estrogens;<sup>27</sup> consistent with our findings, estradiol blood levels in women with regular menstrual cycles generally are not reported to differ by weight.<sup>28-34</sup> Results for estrone are less consistent; significant positive associations with relative body weight have been reported in some,<sup>31,34</sup> but not other,<sup>30,32,35</sup> studies of cycling premenopausal women. Subjects in studies that reported associations with estrone had a wide range of relative body weights, and restriction of subjects in our study to women whose weights for height were 85 to 130 percent of 'desirable' may have limited our chances of observing an association.

We also did not observe associations between the androgens, androstenedione and DHEAS, and body weight. The literature on the relation of androstenedione to body weight in non-hirsute premenopausal women is unclear; obese women have been reported to have higher,<sup>32,34</sup> lower,<sup>33</sup> and not different<sup>30,36-38</sup> blood levels of androstenedione compared with non-obese women. DHEAS levels do not differ by body weight in the majority of studies.<sup>30,32-35,37-39</sup>

Body weight is related consistently inversely to SHBG.<sup>6,28,30,34,35,37</sup> Ingram *et al*<sup>28</sup> also reported a significant positive correlation of proportion of free and albumin-bound estradiol and a negative correlation of SHBG-bound estradiol with BMI in premenopausal

women. Although we observed significantly lower plasma-SHBG levels in heavier women, in our analysis, the amount of estradiol that was SHBG-bound was not associated significantly with weight or BMI.

We observed a significant positive association between height and follicular-phase plasma-estradiol. Adlercreutz *et al.*<sup>40</sup> also recently reported a significant positive correlation between height and follicular-phase plasma-estradiol levels in a comparative analysis of estrogen metabolism in Asian and Caucasian women. Asian women in their study had lower plasma estrogens and tended to be shorter than Caucasians, and the observed correlation between height and estradiol could have been secondary to some other racial difference. In our study, all women were Caucasian.

We are not aware of a physiological mechanism by which height would influence plasma estradiol levels in premenopausal women and the association that we observed could be spurious. When we removed the two short women with low levels of estradiol depicted by the dots in the lower left hand corner of Figure 1 from the analysis, the relation was marginally significant ( $P = 0.06$ ). Additional studies are needed to evaluate further the relation of adult height to plasma hormones and breast cancer risk.

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